

S2-DEFINING RAI REFRACTORY THYROID CANCER: WHEN IS RAI THERAPY UNLIKELY TO ACHIEVE A THERAPEUTIC RESPONSE?

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INTRODUCTION

For more than 50 years, radioactive iodine has been effectively used to treat metastatic thyroid cancer (1). Dramatic therapeutic responses are often seen when the metastatic foci demonstrate high level avidity for radioactive iodine. These dramatic responses are most common in younger patients with well-differentiated papillary thyroid cancer, in whom radioactive iodine therapy produces dramatic shrinkage of structural disease and results in long-term remission's and excellent survival (2). However, radioactive iodine is often much less effective in older patients who often have a larger volume of disease burden and more poorly differentiated tumors that often concentrate radioactive iodine inefficiently. Furthermore, repeated radioactive iodine administrations are often associated with declining therapeutic effectiveness presumably because of a selection for the non-RAI avid components of the tumor to be the persistent disease (2).

Unfortunately, it is often difficult to determine whether or not metastatic thyroid cancer lesions are likely to be responsive to radioactive iodine therapy since significant therapeutic benefit is occasionally seen even in patients with poorly differentiated thyroid cancer, Hürthle cell carcinoma, widely metastatic follicular thyroid carcinoma and occasionally in patients with large volume metastatic foci. Furthermore, the determination of whether or not radioactive iodine has been an effective therapy for an individual patient is also hampered by the observation that metastatic thyroid cancer can progress very slowly over many years and that serum thyroglobulin may continue to decline for years after initial therapy (3, 4).

These clinical conundrums have led to a pattern of multiple, repeated administrations of radioactive iodine over the years that may or may not have been beneficial. More recently, an increased appreciation of the potential side effects of large cumulative doses of radioactive iodine has led to a reevaluation of the therapeutic benefit of radioactive iodine therapy (5). In addition, the recent availability of potentially effective systemic therapies for non-RAI avid metastatic thyroid cancer has led to a wide range of potential new treatment options for these patients (6). As these systemic therapies become increasingly available, it is critically important to determine when therapeutic administration of radioactive iodine is no longer likely to be effective so that these patients can be offered these novel therapies either as part of clinical trials or as standard of care therapy as these agents gain FDA approval.

Ideally, a direct measurement of the RAI dose achieved within each metastatic lesion in every thyroid cancer patient would allow clinicians to confidently determine whether RAI is likely to be tumoricidal (7-9). Unfortunately, lesional dosimetry is not commonly available in clinical practice making it necessary to use a variety of indirect methods to determine if radioactive iodine therapy has been, or is likely to be, effective in the management of individual patients.

In this review, we will review direct and indirect methods that can be used either in clinical practice or in research studies to determine the RAI avidity of metastatic thyroid cancer. Following that review, we will propose criteria that can be used in routine clinical practice to define RAI refractory disease so that patients with non-RAI avid metastatic disease can avoid

excess radioactive iodine administrations that are unlikely to be effective while also minimizing the clinically significant side effects that are associated with large cumulative doses of radioactive iodine.

FACTORS ASSOCIATED WITH SUBOPTIMAL RAI AVIDITY IN METASTATIC THYROID CANCER

As outlined in Figure 1, a wide variety of factors have been shown to be associated with suboptimal RAI avidity in metastatic thyroid cancer. While some of these individual factors may not absolutely define a patient as “RAI refractory”, they do provide important clinical clues as to whether or not additional RAI therapy is likely to have a clinical benefit. Assessment of the RAI avidity of metastatic thyroid cancer can be classified based on direct measurements of lesional dosimetry, indirect predictors of RAI avidity, and/or clinical response to previous RAI therapy.

Figure 1

Factors Associated with Suboptimal RAI Avidity in Metastatic Thyroid Cancer **Direct measurement of lesional dosimetry**

- Therapeutic RAI predicted to deliver individual lesional dose of < 8,000 cGy

Indirect predictors of RAI avidity

- Negative post-therapy RAI scan
 - Following a properly performed administration of > 30 mCi ¹³¹I
 - With either thyroid hormone withdrawal or recombinant human TSH
- Negative diagnostic RAI scan in the setting of structurally identifiable disease
- Markedly positive ¹⁸F FDG PET imaging
- Cumulative RAI administered activities > 500-600 mCi

Response to previous RAI therapy

- Structural disease progression 6-12 months after previous RAI therapy
- Rising serum thyroglobulin 6-12 months after previous RAI therapy

USING LESIONAL DOSIMETRY TO ASSESS RAI AVIDITY

Direct measurement of lesional dose

From a clinical perspective, knowledge of the absorbed dose of radiation to individual metastatic lesions would allow more precise predictions with regard to whether or not radioactive iodine therapy would be expected to be clinically effective. Early studies by Maxon et al demonstrated that lesional absorbed doses of 8000-10,000 cGy (rads) were required to reliably achieve tumoricidal activity (8).

In routine clinical practice, assessment of lesional dosimetry can be done by measuring collimated uptake in selected regions of interest (metastatic foci) which are identified by diagnostic whole body scanning (10). Typically several measurements of the region of interest (and appropriate standard for calibration) are made at discrete time points over time 48-72 hours. When integrated with a careful tumor volume measurement (typically by CT scan), reliable estimates of the concentration of RAI achieved within the metastatic foci can be obtained.

More recently, lesional dosimetry utilizing iodine 124 PET imaging has been the subject of investigation, and if clinically validated, is likely to enter clinical practice in the next few years (9, 11, 12). In this approach, a positron emitting form of radioactive iodine (124 iodine) can be used both for diagnostic imaging but also for determination of the concentration of radioactive iodine within individual lesions using standard PET equipment (See Figure 2). Since 124 iodine is commercially available and standard PET imaging equipment can be used for data acquisition and analysis, assimilation of this technique into clinical practice is likely to be relatively easy once the validation studies are complete and 124 iodine is approved for this indication by the FDA.

Figure 2

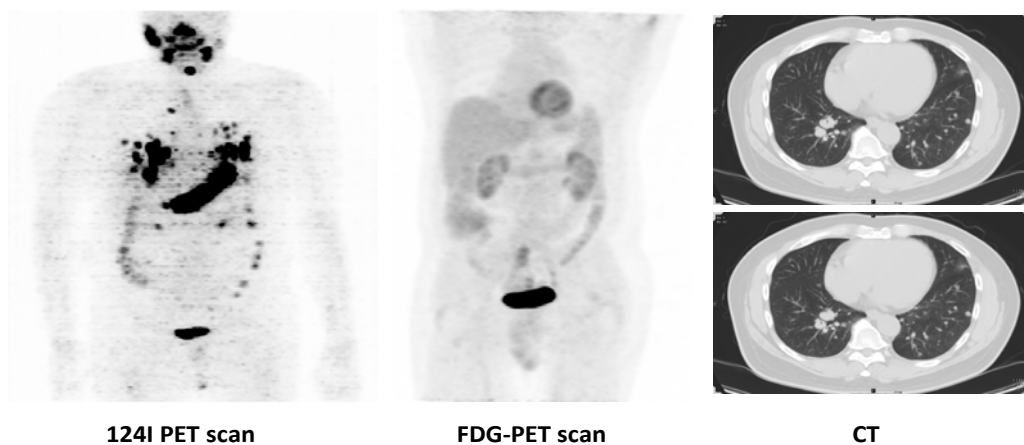


Figure 2. Examples of 124 PET imaging (left panel), FDG PET scan (middle panel) and chest CT (right panel) in a patient with metastatic papillary thyroid cancer

Unfortunately, even when the lesional dose is known for each metastatic foci, clinical decision-making is still complex. Individual patients often demonstrate a wide range of absorbed doses across their metastatic lesions (See Figure 3). Furthermore, heterogeneous dose distributions are often seen within large metastatic lesions (12). Conversely, lesional dosimetry cannot be accurately measured in very small lesions. Additionally, lesional dosimetry estimates can change over time and are therefore required with each subsequent consideration of radioactive iodine therapy (13, 14). Therefore, even if lesional dosimetry is performed, clinical decision-making is still required to determine whether or not additional radioactive iodine therapy is likely to be effective.

Heterogeneity in absorbed dose distribution in individual patient

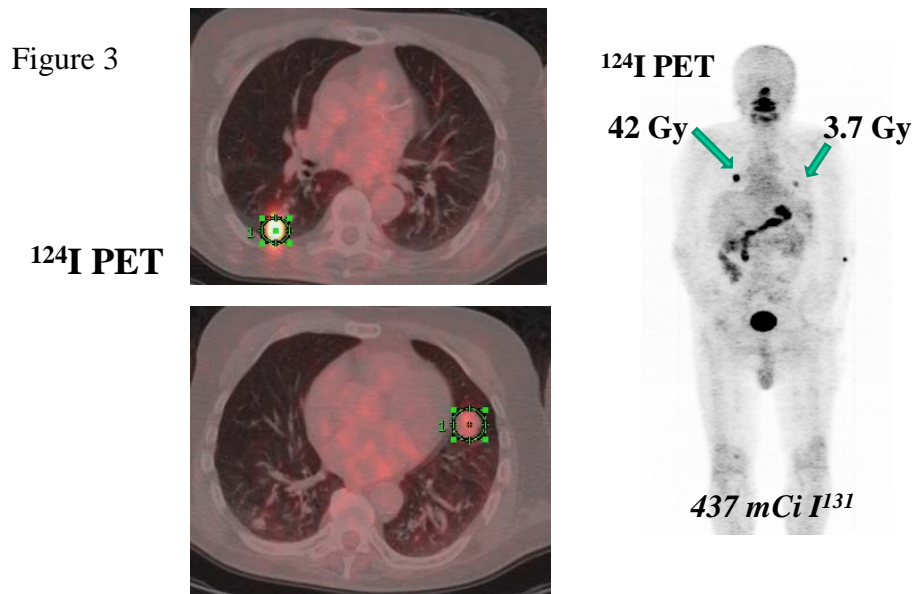


Figure 3. ^{124}I PET lesional dosimetry demonstrating marked heterogeneity in absorbed dose between individual lesions within a single patient.

Nonetheless, lesional dosimetry is often very helpful in determining when radioactive iodine therapy is unlikely to have a therapeutic effect. For example, if all metastatic foci are predicted to receive sub-lethal doses of RAI following the largest safely administered activity of ^{131}I , then radioactive iodine would not be administered. The majority of patients with widespread metastases demonstrate some foci that are very RAI avid and others that are not RAI avid. In this situation, the clinical impact of treating the RAI avid component of the tumor must be assessed clinically. If there is a clinical benefit to treating the RAI avid component of the metastatic disease, then it is reasonable to proceed with additional radioactive iodine therapy. However, if the patient has structurally progressive non-RAI avid metastatic foci, it is possible to classify the patient as having RAI refractory disease for purposes of clinical trials even if clinically insignificant small foci of disease retain RAI avidity.

Indirect correlates of lesional dose

While direct measurements of lesional dosimetry have the potential to provide objective data that can be used to guide treatment decisions, they are not available for the majority of thyroid cancer patients. In clinical practice, radionuclide scanning is often used to provide information about whether or not metastatic lesions are likely to respond to radioactive iodine. The most widely accepted clinical definition of RAI refractory requires demonstration of the lack of radioactive iodine uptake within metastatic lesions on a properly done radioactive iodine post therapy scan obtained after administration of therapeutic doses of radioactive iodine (greater than 30 mCi). While there is some data to indicate that lesional dosimetry can be somewhat higher following thyroid hormone withdrawal preparation than with recombinant human TSH administration in some patients, we accept a negative post therapy scan after recombinant human TSH stimulated radioactive iodine therapy as adequate evidence that the metastatic foci are RAI refractory. The lack of visualization of the metastatic foci after high dose radioactive iodine therapy is certainly a valid and reliable indicator of poor lesional dosimetry.

More recently, Sabra et al demonstrated a lack of therapeutic effectiveness of radioactive iodine in clinical scenarios where structurally identifiable disease was associated with a negative diagnostic whole body scan even when the post therapy scan demonstrated some degree of RAI avidity (15). In our view, the inability to visualize radioactive iodine uptake within structurally significant metastatic foci on the diagnostic 2mCi radioactive iodine scan is an indirect indicator of low absorbed dose. In this situation, even though the metastatic foci can be visualized after high dose therapy, it is quite unlikely that a tumoricidal dose can be achieved since the lesion concentrated radioactive iodine so poorly that it could not be visualized on diagnostic scanning. Internal unpublished data does show that these patients have very low lesional dosimetry when evaluated on 124 iodine PET imaging (See Figure 4).

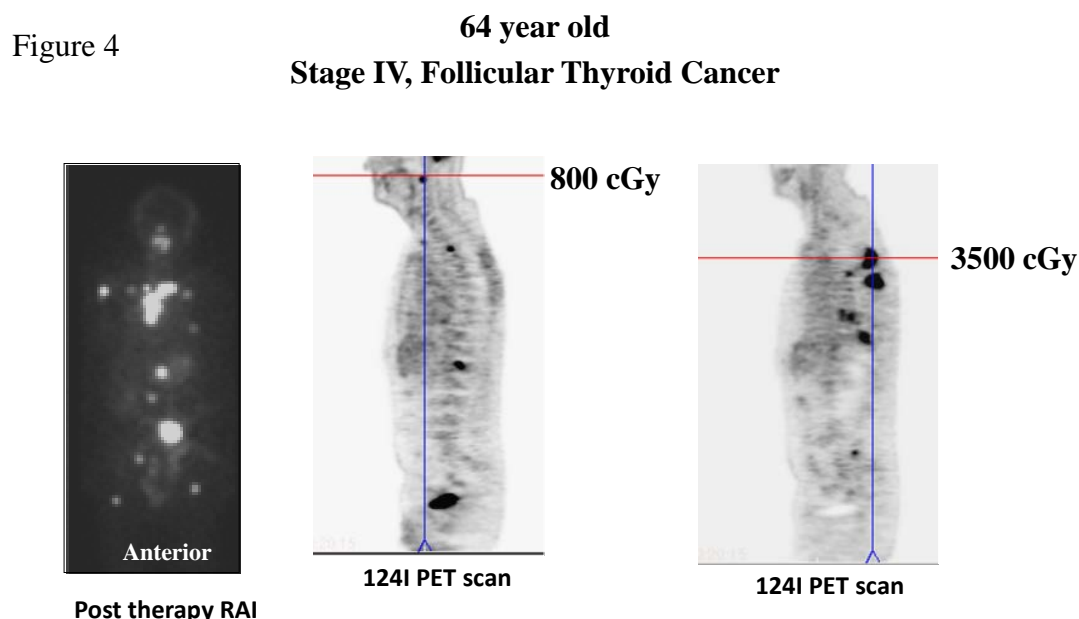


Figure 4. Example of a post therapy RAI scan showing multiple RAI avid skeletal metastases in which lesional dosimetry predicts subtherapeutic doses of RAI (corresponding diagnostic RAI scan was negative).

18 FDG PET scanning can also be used as a predictor of therapeutic effectiveness of radioactive iodine (16). We have previously demonstrated that even high dose radioactive iodine therapy (430 ± 243 mCi cumulative dose) did not decrease the FDG tumor volume, subsequent SUV, or serum thyroglobulin in a cohort of 25 differentiated thyroid cancer with FDG avid metastases (mean maximum SUV 9.3 ± 1 , range 2.3-30) (16). In addition, FDG positivity correlates with structural disease progression and mortality (17). Therefore, we consider patient's that have metastatic foci which have significant FDG avidity (arbitrarily defined as an SUV $> 5-10$), to have disease that is likely to be radioactive iodine resistant, and to progress. We then move on to consideration for novel therapies rather than repeated administrations of radioactive iodine. Conversely, low level FDG avidity (SUV < 2) does not preclude the

possibility that the lesion could be RAI avid and potentially could be responsive to additional RAI therapy.

While the specific histology generally correlates with RAI avidity, none have sufficient sensitivity or specificity to determine whether or not radioactive iodine is likely to be effective therapy. For example, we have seen significant uptake of radioactive iodine in perhaps 10-20% of our patients with either Hürthle cell carcinoma or poorly differentiated phenotypes. Similarly, older patients, particularly with follicular thyroid cancers, often demonstrate the clinical benefit from radioactive iodine therapy. Conversely, it is not uncommon to see metastatic lesions from a classic papillary thyroid carcinoma fail to concentrate significant amounts of radioactive iodine. Therefore, we do not use tumor histology or patient age as primary indicators to define RAI refractory disease.

Similarly, while the molecular profile of radioactive iodine avid metastatic disease differs from that of RAI refractory disease, the molecular profile does not adequately predict a therapeutic response (18, 19). Radioactive iodine refractory disease is enriched in BRAF mutations which have been shown in pre-clinical and clinical models to down regulate the sodium iodine symporter rendering radioactive iodine therapy less effective (20, 21). Even though the significantly higher prevalence of RAS mutations present in RAI avid disease correlates with the likelihood of visualizing metastatic disease on diagnostic RAI scans, the structural response to therapy was not significantly different across the mutational profiles of patient's with RAI avid distant metastases (19).

Large cumulative administered activities of radioactive iodine can also serve as a clinical indicator that additional radioactive iodine therapy is unlikely to be effective. Clinically significant therapeutic effects are very rare in patients that have received a cumulative administered activity of 600 mCi or more (2). Therefore, in the absence of a well documented clinical benefit following the last administered activity of radioactive iodine, it is unlikely that a significant additional therapeutic effect will be seen with cumulative activities exceeding 500-600 mCi.

USING CLINICAL RESPONSE TO PREVIOUS RAI TREATMENTS TO ASSESS RAI AVIDITY

Since it is unusual for a single administration of radioactive iodine to induce remission in patients with metastatic disease, we usually have the benefit of evaluating the effectiveness of the previous radioactive iodine dose when determining whether additional treatments may be helpful. From a clinical perspective, structural disease progression within 6-12 months after a properly administered dose of radioactive iodine would serve as the best evidence that the patient has RAI refractory disease. Once again, it is important to emphasize, that structural disease progression after properly administered RAI therapy constitutes one of the main definitions of RAI refractory disease even if the diagnostic or post therapy scan obtained with the previous treatment was positive. As we have described, planar scanning can identify metastatic lesions even when metastatic foci receive sub-lethal doses of radioactive iodine.

Quite often, the best clinical response to RAI therapy is stable disease. It is usually difficult to determine if the RAI therapy contributed to disease stability, or whether the natural history of an individual patient's disease was destined to be stable/very slow growth even without additional RAI therapy. Therefore, a failure of metastatic lesions to decrease in size after a therapeutic dose does not necessarily mean that RAI therapy was ineffective.

It is worth emphasizing that classification of a patient as radioactive iodine refractory on the basis of response to previous treatments requires a knowledge that the previous treatments

were done correctly. We have seen several instances of patients classified as being unresponsive to radioactive iodine who were consistently iodine contaminated with contrast agents in the days preceding their radioactive iodine therapies. While the details of previous therapies are often not available, it is worthwhile reviewing with the patient their potential exposure to excess iodine either through the diet or medical imaging, their method of preparation for radioactive iodine therapy, and the timing of the imaging following radioactive iodine therapy.

While serum thyroglobulin is one of the key components to response to therapy assessments, recent data demonstrates that serum thyroglobulin values may continue to fall for years after initial therapy (3, 4). This has been demonstrated both following radioactive iodine remnant ablation (22), and subsequent to therapeutic doses of radioactive iodine in pediatric thyroid cancer (3). Therefore, rising thyroglobulin values 6-12 months after a therapeutic dose of radioactive iodine would provide biochemical evidence that the previous administered activity of RAI was suboptimally effective.

PRACTICAL CLINICAL DECISION MAKING: DEFINING RAI REFRACTORY DISEASE

In the ideal world, direct measurements utilizing either collimated uptake in selected regions of interest or 124 PET technology would be used to define RAI refractory disease as metastatic foci that would achieve a lesional dose < 8,000 rads after therapeutic administration of RAI.

However, since lesional dosimetry is usually not available in most clinical situations, the definition of RAI refractory disease in most patients will rely on documentation of:

1. A negative post-therapy RAI scan after a properly administered RAI therapy
2. Structural disease progression within 6-12 months of a properly administered RAI therapy
or
3. Rising serum thyroglobulin within 6-12 months after a properly administered RAI therapy

Furthermore, while not definitively classifying a patient as being completely refractory to RAI, the following clinical factors make it much less likely that RAI therapy will achieve a clinically significant therapeutic response:

1. A negative diagnostic whole body RAI scan in the setting of structurally identifiable disease
2. A positive FDG PET scan with an SUV > 5-10
3. Cumulative administered activities of > 500-600 mCi RAI.

CONCLUSIONS

In the future, we are hopeful that more widespread use of lesional dosimetry will lead to better decision making with regard to be able to objectively define RAI refractory disease. Until then, it will be necessary to continue to define RAI refractory disease on the basis of indirect predictors of RAI avidity and clinical assessments of the effectiveness of previous RAI therapies.

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